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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,504	10/18/2000	Marc K. Wallack	11221/5	5100

26646 7590 07/01/2003

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 07/01/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/691,504

Applicant(s)

Wallack et al.

Examiner

Anne Marie Wehbé

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Apr 17, 2003
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-107 is/are pending in the application.
- 4a) Of the above, claim(s) 1-17, 24, 25, 27, 28, 39-54, 65, 66, 68, 69, 97, 99 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Applicant's amendment and response received on 4/17/03 has been entered. Claims 1-107 are pending in the instant application. This application contains claims 1-17, 24-25, 27-28, 39-54, 65-66, 68-69, 97-98, and 100-101 drawn to subject matter non-elected with traverse in paper nos. 11, and 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 are currently under examination at this time. An action on the merits follows.

Claim Rejections - 35 USC § 112

The rejection of claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action stated that the specification, while being enabling for methods of generating an anti-tumor immune response and methods of inhibiting tumor growth in a mammal comprising the administration at or near a regional lymph node of an immunogenic composition comprising a recombinant vaccinia virus encoding IL-2 and autologous or syngeneic

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DCs or DC/MNs pulsed with an antigen preparation comprising enucleated cytosol and cell membranes from tumor cells infected with a recombinant vaccinia virus encoding IL-2, wherein the antigen preparation is derived from tumor cells which the same tumor cells or the same type of tumor cells present in the mammal, does not reasonably provide enablement for said methods and immunogenic compositions wherein the immunogenic composition comprises any type of antigen presenting cells pulsed with tumor lysate from any type of tumor, or wherein the immunogenic composition is administered to any location in the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The applicant argues that the claims have been amended to recite antigen presenting cells, "which are capable of inducing T-cell activation", and that the specification teaches that lymphoid cells, including dendritic cells, B cells, and monocytic cells are capable of inducing T cell activation. In response, the previous office noted that at the time of filing, the dendritic cell had been identified as the crucial antigen presenting cell for priming T cells. The previous action cited Pardoll for teaching that, "Because DCs are felt to be the primary cell necessary for activating virgin T cells, their role in priming immunologic responses is now considered central" (Pardoll, page 528, column 1). Pardoll teaches that the particular potency of dendritic cells in activating T cells derives from the fact that these cells express 50-fold higher levels of MHC molecules than macrophages and other antigen presenting cells, they express extremely high levels of T cell adhesion and co-stimulatory molecules, and they express T cell specific chemokines (Pardoll, page

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530, column 1). Thus, it is clear that the art at the time of filing considered presentation of antigen by professional antigen presenting cells, and dendritic cells in particular, as essential for priming an antigen-specific T cell response. It was further noted in the previous office action that the applicant's working examples in mice and in humans are limited to the use of cultured dendritic cells or dendritic/monocytic cells. The specification fails to provide sufficient guidance for using antigen presenting cells other than dendritic/monocytic cells. Therefore, based on the state of the art of priming T cells, the unique features of the dendritic cell, the limitation of the working examples to dendritic/monocytic cells, and the breadth of the claims, it would have required undue experimentation to practice the instant invention with any antigen presenting cell, even antigen presenting cells, "capable of inducing T cell activation".

The applicant further argues that the claims have been amended to recite wherein the cells are autologous, syngeneic, or allogeneic, and that the specification provides sufficient guidance for using allogeneic cells, citing pages 13 and 19, specifically example 1. Page 13 of the specification does not mention allogeneic cells. Page 13 in fact states that, "preferably, antigen presenting cells are obtained from the patient". Page 14, however, does disclose using HLA-matched donor dendritic cells and/or monocytic cells, page 14, lines 12-13. The working examples provided utilize autologous or syngeneic cells, thus avoiding the rejection issue. The examples provide no guidance or evidence which demonstrates that allogeneic or xenogeneic DCs pulsed with tumor lysate are capable of persisting in a transplanted immunocompetent host for a sufficient period of time to generate and sustain anti-tumor immune responses. Example 1, and

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page 19 of the specification does not recite the use of allogeneic dendritic cells. Page 17 of the specification describes the cells used in example 1, they are dendritic and monocytic cells isolated from spleens from the same mouse strain. Thus, the cells used were syngeneic not allogeneic. Page 19 does not disclose using allogeneic cells. Further, example 2 uses autologous dendritic cells, see page 25, lines 26-30. Therefore, the teachings in the specification are limited to a single statement that HLA-matched dendritic cells may be used. The previous office action provided a detailed analysis concerning the rapid rejection of allogeneic tissue. Further, the claims as written are not limited to HLA-matched allogeneic cells, but read on any allogeneic APC which may or may not share any of the same MHC haplotypes as the host. Thus, based on the nature of allogeneic transplant rejection, the lack of guidance or working examples concerning the administration of allogeneic cells in the specification, and the breadth of the claims, it would have required undue experimentation to practice the full scope of the invention as claimed.

In regards to the issue of tumor antigens, the applicant argues that the MAGE gene family represent "shared" tumor antigens and the Pardoll et al., cited by the office, teaches that the MAGE family of antigens are expressed in melanoma and other tumors. The applicant also argues that the specification provides a working example which used MAGE antigens. In response, it is noted that the claims as written are not limited to melanoma tumor cell oncolysates which contain a MAGE gene family antigen for generating anti-melanoma immune responses. The claims read on the use of any tumor lysate to induce an immune response capable of treating any type of cancer, including cancers which do not express any of the antigens present in the tumor lysate.

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The previous office action stated that the specification does not provide any guidance regarding the ability of immune responses generated against any tumor antigens present in tumor lysate to protect against the growth of a tumor which does not express the antigens present in the tumor lysate. At the time of filing, it was well-known that most types of tumors express tumor antigens which are unique to either the particular tumor, or tumor type (Pardoll, page 526). While the idea of "shared" tumor antigens exists in the literature, there is little data to support the concept. The specification does not teach tumor cells which express "shared" tumor antigens or identify and particular "shared" antigens. Further, while Pardoll does teach that MAGE antigens are expressed in breast cancer in addition to melanoma, Pardoll does not teach that shared antigens are known which are capable of treating any and all cancers, or teach any other tumor antigens other than MAGE which are not exclusively linked to a particular form of cancer. In addition, the specification's working examples pulse the DCs with tumor oncolysate from the either the same tumor present in the host, or with tumor cells which are the same class of cells as the host tumor- see for example the description of the clinical trial in patients with melanoma which received autologous DC/MCs pulsed with oncolysate from established human melanoma cell lines. The specification provides insufficient guidance and evidence to enable the treatment of tumors in a host by administering DCs or DC/MCs pulsed with tumor lysate from a tumor which does not express any of the same tumor antigens as the host tumor.

In regards to routes of administration, the applicant argues that the specification lists various routes which can be used to deliver the pulsed APCs and that the teachings of Nestle are

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only representative of one researcher's choice concerning routes of administration. In response, the previous office action stated that the specification also does not provide an enabling disclosure for administering the disclosed immunogenic compositions by any route of administration to any site in the mammal to be treated. The specification's working examples inject the immunogenic compositions at or near the site of major peripheral lymph nodes. The specification does not provide sufficient guidance for priming therapeutic immune responses with the cells and virus of the instant invention using any route and site of administration. At the time of filing, it was well-known that T cell priming occurs in the lymph nodes. In order for dendritic cells to prime a naive T cell, it must first migrate to a lymph node (Nestle et al., page 328). Nestle et al. teaches that, "[i]njecting DCs in a peripheral tissue site (such as skin) or intravenously may lead to a substantial loss of DCs during migration into spleen or lymph node" (Nestle et al., page 328, column 2). While Nestle uses the word "may", Nestle's teachings regarding the behavior of dendritic cells and the nature of T cell priming provide evidence of the state of the art of dendritic cell vaccination at the time of filing. Nestle et al. therefore clearly teaches the unpredictability of generating anti-tumor immune responses by administering antigen pulsed DCs in locations other than near or at a lymph node. Thus, based on the nature of T cell priming, the nature of dendritic cell migration, the art recognized unpredictability of priming immune responses using intradermal, subcutaneous, or intravenous administration of dendritic cells, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the full scope of the invention as claimed.

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The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Ultimately, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). For the reasons discussed in detail above, the specification only provides an enabling disclosure for methods of generating an anti-tumor immune response and methods of inhibiting tumor growth in a mammal comprising the administration at or near a regional lymph node of an immunogenic composition comprising a recombinant vaccinia virus encoding IL-2 and autologous or syngeneic DCs or DC/MNs pulsed with an antigen preparation comprising enucleated cytosol and cell membranes from tumor cells infected with a recombinant vaccinia virus encoding IL-2, wherein the antigen preparation is derived from tumor cells which are the same tumor cells or the same type of tumor cells present in the mammal.

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The rejection of claims 56-59 and 80-81 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the skilled artisan would understand that the ranges provided are meant to encompass plaque forming units which are not precisely, for example, 10,000 PFU-10,000,000 PFU. The applicant further argues that Federal Circuit in *Eiselstein v. Frank* held that the meaning of "about" is fact specific for each case, based on the nature of the invention and the knowledge of the skilled artisan. In the instant case, the specification does not define how much of a difference in PFU from say 10,000 PFU would be encompassed by the term "about". Further, at the time of filing, the skilled artisan regularly used specific PFUs to indicate dosages and ranges. PFUs is determined by serial dilution of the virus, as such the results are typically determined in powers of 10. It is unclear from the specification what deviation from the low and high end PFUs recited are encompassed by the claims in view of the use of the term "about".

Claim Rejections - 35 USC § 103

The rejection of claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 under 35 U.S.C. 103(a) as being unpatentable over Nestle et al. (1998) Nat. Med., Vol. 4, No. 3, 328-332 in view of Sivanandham et al. (1994) J. Immunol. Immunother., Vol. 38, 259-264, is maintained.

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Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that neither Nestle et al. nor Sivanandham et al. teach a 2-part vaccine as recited in the instant claims. Therefore, the applicant concludes that the combination of references fails to teach or suggest the claimed invention. In response, it appears that applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is further noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). The examiner further recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the

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art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In the instant case, Nestle et al. was cited for teaching methods of vaccinating human patients with patient-derived dendritic cells pulsed with melanoma tumor lysate, wherein 10X6 tumor lysate pulsed dendritic cells are injected into inguinal lymph nodes, and wherein the dendritic cells express at least 2 HLA class I A antigens (Nestle et al., page 328, and page 329, Table 1). The previous office action acknowledged that Nestle et al. differs from the instant invention by not teaching that the dendritic cells are pulsed with tumor lysate from tumors infected with VV-IL2, and that the pulsed dendritic cells are administered with separate VV-IL-2.

Sivanandham et al. was further cited to supplement Nestle et al. by teaching that vaccinia oncolysate prepared from VV-IL-2 infected colon tumor cells is superior to oncolysate alone in generating anti-tumor immune responses (Sivanandham et al., page 262, Figures 3 and 4). Motivation to combine the teachings of Nestle and Sivanandham is found in Sivanandham's teaching that vaccinia oncolysate prepared from VV-IL-2 infected colon tumor cells is superior to oncolysate alone in generating anti-tumor immune responses. Thus, based on the motivation provided by the teachings of Sivanandham et al., that oncolysate prepared from tumor cells infected with VV-IL-2 is more immunogenic, it would have been *prima facie* obvious to the skilled artisan to substitute vaccinia oncolysate prepared from VV-IL-2 infected tumor cells for the uninfected tumor lysate taught by Nestle et al. in Nestle's methods of treating tumors by administering DCs pulsed with tumor lysate. Based on the increased efficacy of the lysate taught

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by Sivanandham et al. in inducing immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor immune responses *in vivo* by administering dendritic cells pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells.

Sivanandham et al. was further cited for teaching that the co-administration of viral oncolysate and exogenous IL-2 improves immune responses compared to the administration of viral oncolysate alone (Sivanandham et al., page 262, Figure 3). While Sivanandham et al. teaches the administration of recombinant IL-2 with viral oncolysate, the skilled artisan would have been motivated to use the VV-IL-2 also taught by Sivanandham instead of the recombinant IL-2 to limit systemic IL-2 toxicity and to prolong the exposure of the mammal to IL-2, since Sivanandham teaches that recombinant IL-2 has a short half-life and causes toxicity in humans (Sivanandham et al., page 260, column 1). The skilled artisan would have had a reasonable expectation of success in using directly injected VV-IL-2 to stimulate immune responses based on the data presented by Sivanandham et al. that direct injection of 2×10^6 pfu of VV-IL-2 decreases tumor burden compared to controls (Sivanandham et al., page 262, Figure 3). Thus, it would have been *prima facie* obvious to the skilled artisan at the time of filing to supplement the administration of DCs pulsed with vaccinia oncolysate with the direct administration of VV-IL-2 in order to increase anti-tumor immune responses. Based on the teachings of Sivanandham et al. that IL-2 improves immune responses to oncolysate, and that VV-IL-2 induces anti-tumor immune responses, the skilled artisan would have had a reasonable expectation of success in

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generating anti-tumor immune responses by combining the administration of DCs pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells with the administration of VV-IL-2. The applicant is further reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be

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directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Anne M. Wehbé', with a stylized, flowing script.